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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,162	09/22/2003	Ronald R. Breaker	25006.0016U2	4368

23859 7590 07/10/2007

NEEDLE & ROSENBERG, P.C.
SUITE 1000
999 PEACHTREE STREET
ATLANTA, GA 30309-3915

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
07/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/669,162	BREAKER ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *8-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 4-26-07.

Claims 1-21 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

This application contains claims 8-19, drawn to an invention nonelected with traverse in the election filed 10-23-06. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 1-7, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 12-12-06.

Applicant's arguments filed 4-26-07 have been fully considered but they are not persuasive. Applicant argues that adequate written description has provided for the

genus of nucleic acid molecules claimed because the specification provides numerous examples of structural features and sequence relationships of riboswitches, and provides description of the key structural features and sequence relationships necessary for the operation of riboswitches in general. Applicant also argues that the concensus sequences provided clearly demonstrate possession of the broad general subject matter of the present claims. Applicant additionally argues that consensus elements of other guanine aptamers in guanine responsive riboswitches have been provided and that one of skill in the art would have been able to readily produce functional riboswitches and the riboswitch can comprise any aptamer.

Contrary to Applicant's assertions, the very broad genus of molecules claimed, comprising regulatable gene expression constructs comprising riboswitches that are activated by a trigger molecule and produce a signal upon activation, and which constructs further comprise any control strand, any aptamer domain, and any expression platform domain comprising a regulated strand, has not been adequately described. This very broad genus encompasses a vast array of molecules and combination of subunits or component parts, and the disclosure fails to provide a representative number of species for the very broad genus which provide for the functions claimed, of regulating expression of a nucleic acid strand, and which riboswitches produce a signal upon activation by a trigger molecule.

The specification teaches the 5'-UTR of the *B. subtilis* xpt-pbuX mRNA as a potential guanine-specific riboswitch (figures 24-26 of the instant specification). The specification also teaches a comparison between this 5'-UTR fragment (of 185

nucleotides) and other bacterial sequences, whereby a purportedly conserved RNA motif, termed a "G box" has been identified as domain for a guanine-riboswitch, suggesting that conserved secondary and tertiary structures are likely a pre-requisite for adopting the required, yet undefined three-dimensional fold necessary for riboswitch function (see e.g. p. 139 of the instant specification). The specification also discusses the ability of hypoxanthine, xanthine and adenine to also effect target nucleic acid cleavage under various conditions with this 5'-UTR fragment.

The examples given, and the generic descriptions of riboswitches, comprising an aptamer domain and an expression platform, the generic descriptions of structure function relationships for some identified (and proposed) stem structures of platform domains, and the sequence comparisons between previously described riboswitches found in nature, and sequence data bases, together do not provide the concise structural features required for the very broad genus of compounds claimed. Applicant asserts that those of skill in the art would have been able to readily produce functional riboswitches using what is known in the art. But to satisfy written description requirements, Applicant must be in possession at the time of filing of an adequate representation of species for the broad genus of compounds claimed, and not merely have the ability to screen for such species. For these reasons, the instant rejection is maintained.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of searching for candidates of the

genus comprising RNA comprising any riboswitch operably linked to a coding region, which riboswitch regulates expression of the RNA, and which riboswitch and coding region are heterologous to each other, and which riboswitch comprises an aptamer domain, a control strand and an expression platform domain comprising a regulated strand, and which regulated and/or control strands form a stem structure, and which riboswitch is optionally derived from a naturally occurring guanine-responsive riboswitch, and which riboswitch is activated by a trigger molecule and produces a signal upon activation by the trigger molecule, does not reasonably provide enablement for predictably making and designing the members of the broad genus of molecules claimed without undue experimentation for the reasons of record set forth in the Office action mailed 12-12-06.

Applicant's arguments filed 4-26-07 have been fully considered but they are not persuasive. Applicant argues that the claims are fully enabled and that one of skill in the art would have been able to create, make and use the genus of constructs claimed because the art teaches various allosteric mechanisms that certain mRNAs use to regulate gene expression in response to various metabolites. Applicant also argues that the generic primary and secondary structural features of riboswitches are described in the instant specification and no further guidance is needed to produce the broad genus of molecules claimed.

Contrary to Applicant's assertions, it would require undue experimentation beyond that taught in the instant specification, to produce the broad genus of compounds claimed, which encompasses RNA comprising any riboswitch operably

linked to any coding region, which riboswitch regulates expression of any RNA, and which riboswitch and coding region are heterologous to each other, and which riboswitch comprises any aptamer domain, any control strand and an expression platform domain comprising a regulated strand, and which regulated and/or control strands form a stem structure, and which riboswitch is optionally derived from any naturally occurring guanine-responsive riboswitch, and which riboswitch is activated by a trigger molecule and produces a signal upon activation by the trigger molecule. The art teaches various allosteric mechanisms that certain mRNAs reportedly use to regulate gene expression in response to various metabolites, including thiamine pyrophosphate and lysine respondent mechanisms that affect thiamine and lysine biosynthetic processes respectively.

Contrary to Applicant's assertions, Applicant has not provided guidance in the specification toward a method of making and using a representative number of species of the expansive genus of molecules claimed. The specification teaches the identification of a 5'-UTR fragment of the *B. subtilis* xpt-pbuX mRNA as a potential guanine-specific riboswitch (figures 24-26 of the instant specification), as well as teaching a comparison between this 5'-UTR fragment (of 185 nucleotides) and other bacterial sequences, whereby a purportedly conserved RNA motif, termed a "G box" has been identified as a domain for a guanine-riboswitch, suggesting that conserved secondary and tertiary structures are likely a pre-requisite for adopting the required three-dimensional fold necessary for riboswitch function (see e.g. p. 139 of the instant specification). The ability to test various sequences for their ability to cleave target

nucleic acid strands in the presence of various ligands, and the postulation of required, yet undefined structural constraints for riboswitch activities is not representative of the ability to predictably make and use the broad genus of compounds claimed. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with determining the necessary sequence and structural components for designing functional riboswitches encompassed by the very broad genus claimed.

And, contrary to Applicant's assertions, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of sequence and structural characteristics, by trial and error, based on the identification and characterization of a representative number of species of the genus of compounds claimed, whereby riboswitches are identified, designed and constructed. The examples provided do not enable one to make and use the broad genus of compounds claimed without undue experimentation. And patent is not a hunting license, or an invitation for further experimentation. For these reasons, the instant rejection is maintained.

Claims 1-7 and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Breaker (Curr. Opin. Biotech., 13: 31-39, Feb. 1, 2002) for the reasons of record set forth in the Office action mailed 12-12-06.

Applicant's arguments filed 4-26-07 have been fully considered but they are not persuasive. Applicant argues that the teachings of Breaker do not properly anticipate the instant invention because Breaker does not disclose the elements of the claimed

riboswitch molecule, but instead discloses a ribozyme. Applicant argues, for instance, that the instantly claimed riboswitches comprise P1 stems as control elements of the aptamer, and that Breaker does not teach such control elements. Applicant is arguing limitations that are not in the claims.

Contrary to Applicant's assertions, Breaker properly anticipates the instant invention. Breaker, for instance teaches nucleic acid constructs containing biosensor elements recognized by RNA molecular switches (see second full paragraph on p. 31 of Breaker). See also first full paragraph on p. 32, describing RNA molecules that respond allosterically to chemical signals such as ATP. Breaker teaches gene expression constructs comprising the elements claimed, e.g. a riboswitch, derived from either a naturally occurring or a non-naturally occurring riboswitch, operably linked to a coding region, which riboswitch comprises an aptamer domain and an expression platform domain, which aptamer domain comprises a P1 stem, which P1 stem comprises an aptamer strand and a heterologous control strand, and the expression platform comprises a regulated strand, and which regulated or control strand forms a stem structure, and which riboswitch produces a signal when activated by a guanine trigger molecule (see the text on p. 31; fig. 2 on p. 33; fig. 3 on p. 34; text on p. 38).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating

to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
7-6-07

TC1600

JANE ZARA, PH.D.
PRIMARY EXAMINER